

CALCIUM AND VITAMIN D STATUS OF PREGNANT TEENAGERS IN MAIDUGURI, NIGERIA

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This study investigates parameters related to calcium and bone metabolism by determining the concentrations of total calcium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, parathyroid hormone, and phosphorous in young pregnant women. The patient population was 30 pregnant Nigerian teenage women grouped by trimester (10 per group), 10 women immediately following delivery, and 21 healthy age-matched controls. On the basis of serum prealbumin levels, the general nutrition of the pregnant women was found to be significantly below that of the more privileged and better-educated nonpregnant controls. The mean total calcium concentration in sera of the third-trimester women was 8.83 mg/dL, which was significantly below that of the controls (9.77 mg/dL) and the first-trimester group (9.30 mg/dL). Despite the 10% to 15% decline in the serum level of total calcium during pregnancy, the parathyroid hormone level decreased markedly from 0.60 to 0.61 ng/mL in the first and second trimesters to 0.41 ng/mL in the third trimester. Serum vitamin D and 1,25-dihydroxyvitamin D levels in the second and third trimesters were within the normal range. These data indicate that toward the end of gestation, pregnant teenagers in northern Nigeria appear to become calcium deficient and do not exhibit the expected increase in serum parathyroid hormone levels normally seen in pregnant women. (*J Natl Med Assoc.* 1997;89:805-811.)

Key words: calcium ♦ vitamin D ♦ pregnancy
♦ nutrition

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The incidence of obstructed labor from cephalopelvic disproportion is high among impoverished populations, especially in communities in which childbearing commonly occurs in the early teenage years, before full physical maturity has been attained. In 1985, Harrison¹ analyzed 22,774 consecutive pregnancies and 22,725 deliveries at the Ahmadu Bello University Hospital in Zaria, Nigeria. He found cephalopelvic disproportion to be the second most frequent significant pregnancy complication and the leading cause of maternal and neonatal mortality. Furthermore, the prevalence of cephalopelvic disproportion was highest among the youngest teenagers, and their mortality rate (30%) was far higher than that of any other group of parturient women. In addition, among the pregnant

teenagers, the threat to fetal survival was even greater than the risk to maternal health.

Harrison¹ attributed the high prevalence of cephalopelvic disproportion in the teenage group to extreme pelvic contraction and incomplete skeletal maturation of the pelvis. Moerman² has shown that even at 16 years of age, skeletal growth is far from complete and that the bony pelvis is less mature than maternal height would suggest. He postulated two reasons for this: first, development of the bony birth canal is slower than that of maternal height, especially during the early teenage period, and second, because the canal does not reach mature size until 2 to 3 years after cessation of vertical growth.² Labor and delivery problems related to skeletal growth in teenagers in underprivileged societies could be exacerbated by nutritional deficiencies (eg, calcium and vitamin D) and by the increased demands imposed by lactation.

Although more than 10 years have elapsed since the Zaria study¹ was published, little attention or follow-up has been given to the questions raised about the cause of the high prevalence of cephalopelvic disproportion in pregnant teenagers in northern Nigeria. Having recently conducted a study of serum and vitamin D levels in rachitic children in Jos, Nigeria, a city located not far from Zaria, and having found evidence of a defect in the vitamin D-endocrine system of these children,^{3,4} we set out to assess the calcium and vitamin D status of pregnant teenagers in northern Nigeria. Specifically, the levels of the following substances in the blood serum of 10 pregnant teenagers were determined during each of the three trimesters of pregnancy and the data were compared with the corresponding values of 21 age-matched, nonpregnant controls: calcium, phosphorous, 25-hydroxyvitamin D, parathyroid hormone, and 1,25-dihydroxyvitamin D.

METHODS

Study groups were comprised of 14- to 20-year-old women who were attending maternity clinics at the University of Maiduguri Teaching Hospital and the State Specialist's Hospital in Maiduguri, Nigeria. Serum specimens were collected between July 4 and July 25, 1994. Pregnant subjects were subdivided into three groups based on trimester. The control group was comprised of 21 healthy, age-matched, nonpregnant women. In addition, 10 women at delivery formed a fourth experimental group. The study was approved by the Ethics Review

Committee of the University of Maiduguri Teaching Hospital, and informed consent was obtained from each participant prior to sample collection.

Venous blood from the mothers was collected into 10-mL vacutainer tubes. In the case of the parturients, fetal blood also was collected by drawing blood from the umbilical vein of the placenta. After 45 minutes, the tubes were cooled on ice and centrifuged for 8 minutes. The serum layer was separated and aliquotted into Eppendorf microcentrifuge containers that were immediately frozen (-43°C) for 1 to 6 weeks until they were transported to Albuquerque, New Mexico for analysis.

Nutritional status was evaluated using several parameters. The serum prealbumin concentration, which is useful in determining the adequacy of recent protein intake (in the absence of liver disease), was determined using a commercially available kit (N Prealbumin Kit, Behring, Somerville, New Jersey). Albumin was determined by the method of Doumas et al⁵ using bovine serum albumin as the standard. Total protein was estimated by the method of Bradford⁶ using bovine serum albumin as the standard. Limitations in the technical capabilities at the site where the blood samples were obtained prevented us from estimating free calcium. The total serum calcium concentration was quantified using an automated dry chemical slide method based on Arsenazo III dye-binding. 25-hydroxycholecalciferol (25-hydroxyvitamin D) was analyzed by a radioimmunoassay using a ^{125}I tracer, and 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D) was determined using a radioreceptor assay procedure and a ^3H -tracer. The serum content of parathyroid hormone was estimated using a radioimmunoassay.

The Number Cruncher Statistical System program (Version 5, NCSS, Kaysville, Utah) was used to perform the statistical analyses, and group comparisons were made using the Mann-Whitney two-sample test.

RESULTS

Table 1 summarizes some of the salient characteristics of the 21 nonpregnant women who served as controls and the 30 pregnant women who were grouped, 10 each, by trimester. The mean age of the women in each of the three experimental groups did not differ statistically from that of the control group (17 years). Only 3 of the 30 pregnant women were 20 years old; all of the other women were between the ages of 14 and 19 years. The mean maternal

Table 1. Patient Characteristics

Characteristic	Controls (n=21)	Pregnant Teenagers					
		1st Trimester (n=10)	P Value	2nd Trimester (n=10)	P Value	3rd Trimester (n=10)	P Value
Age (years)	17 (9.32)*	16 (3.35)	NS	18 (3.10)	NS	18 (2.62)	NS
Height (meters)	1.63 (0.09)	1.60 (0.10)	NS	1.66 (0.08)	NS	1.59 (0.08)	NS
Weight (kg)	48.8 (8.2)	50. (6.37)	NS	60.0 (15.9)	NS	65.9 (8.26)	.0005
Midarm circumference (cm)	23.8 (2.48)	23.3 (2.29)	NS	23.2 (1.79)	NS	22.4 (3.55)	NS
Prealbumin (mg/dL)	28.1 (3.95)	20.9 (4.37)	.0005	19.9 (3.66)	.0005	23.1 (2.75)	.0001
Albumin (g/dL)	6.97 (0.33)	6.46 (0.48)	.01	6.14 (0.19)	.0005	5.97 (0.27)	.0005
Total protein (g/dL)	8.88 (0.99)	8.63 (1.05)	NS	8.28 (1.11)	.03	8.19 (0.51)	.01

Abbreviations: NS=not significant.
*Numbers in parentheses indicate one standard deviation.

weight gain during gestation was approximately 17 kg, which is expected for a normal pregnancy.

The results of the serum prealbumin determinations (Table 1) revealed that the general nutrition of the control group, which was comprised of nonpregnant teenagers, was superior to that of the pregnant women; the mean prealbumin value of the controls (28.1 mg/dL) was significantly higher ($P<.001$) than that of the pregnant women at all three stages of pregnancy (mean values: 19.9 to 23.1 mg/dL). The lower limit of the reference range for prealbumin at the University of New Mexico Health Science Center is 20 mg/dL. Although the weights of the pregnant teenagers at each stage of pregnancy were reasonable for healthy women, the fact that their serum prealbumin levels were at the margin of the lower limit of the reference interval suggests that their overall nutrition was suboptimal at the time of the study.

The mean prealbumin level of the cord sera of the fetuses was two thirds that of the mean prealbumin level of the sera of the mothers who delivered them (Table 2). As there are few published reports of fetal prealbumin concentrations, there is little we can say about the values found in the Nigerian fetuses relative to populations in other parts of the world. However, when the serum prealbumin value of each mother was plotted versus the corresponding value of the paired fetus, no correlation ($P>.05$) was observed. This lack of correlation implies that the fetal level of prealbumin is not strongly influenced by the general nutritional status of the mother.

Serum Calcium, Phosphorus, Parathyroid Hormone, and Vitamin D Levels in Pregnant Women as a Function of Trimester

The total calcium concentration of the control group, which was comprised of nonpregnant teenage women, was 9.77 mg/dL (Table 3), well within the normal reference interval for healthy women (9 to 10.3 mg/dL). However, there was a progressive decrease in the concentration of total calcium throughout pregnancy, such that by the third trimester and at the time of delivery (Table 2), the mean calcium level was <9 mg/dL, which is the lower limit of normal. Even in the face of the fluid expansion associated with pregnancy, the total serum calcium level of pregnant women in North America and Europe usually does not fall below 9 mg/dL. Furthermore, in another study conducted recently in Jos, Nigeria (R.H. Glew, October 1997) of pregnant women in the age range 20 to 29 years, the total calcium levels at the time the women delivered were between 9.2 and 9.5 mg/dL. Thus, the pregnant teenagers reported herein appear to have progressed to a mild hypocalcemic state by the third trimester. Furthermore, considering that the lower limit of normal for serum phosphorous is 4.5 mg/dL,⁷ all of the teenage women who participated in the present study appear to have been markedly hypophosphatemic throughout pregnancy.

As shown in Table 3, the serum 25-hydroxyvitamin D levels increased two- to three-fold between the first and third trimesters, while the 1,25-dihy-

Table 2. Comparison of Serum Calcium and Vitamin D-Related Parameters in Teenage Mothers and Their Fetuses at Delivery

Parameter	Mothers (n=10)	Fetuses (n=10)	P Value	Fetal/ Maternal Ratio*
Prealbumin (mg/dL)	20.3 (4.44)†	13.4 (2.9)	.0005	0.66
Total calcium (mg/dL)	8.78 (0.39)	10.8 (0.33)	.00	1.23
Phosphorous (mg/dL)	3.62 (0.81)	5.37 (0.79)	.0005	1.48
Parathyroid hormone (ng/mL)	0.52 (0.17)	0.36 (0.11)	.03	0.69
25-hydroxyvitamin D (ng/mL)	17.8 (9.14)	13.2 (7.72)	NS	0.74
1,25-dihydroxyvitamin D (pg/mL)	130 (37.7)	66.1 (15.8)	.0005	0.51

Abbreviations: NS=not significant.

*Fetal values represent umbilical cord blood values.

†Numbers in parentheses indicate one standard deviation.

droxyvitamin D level rose by about 30%. Most surprisingly, however, was the finding that in the face of a 10% to 15% decline in the serum total calcium concentration, the parathyroid hormone level of the mothers did not increase as one might expect,⁸⁻¹⁰ but instead decreased by 50% between the second and third trimesters.

Comparison of Maternal and Cord Blood Levels of Calcium, Phosphate, Parathyroid Hormone, and Vitamin D

In addition to analyzing the blood serum of pregnant women, calcium- and vitamin D-related parameters were compared between mothers and their fetuses at the time of delivery (Table 2). The fetal/maternal ratios of the serum calcium and phosphorus concentrations were 1.23 and 1.48, respectively. As was observed in the third-trimester pregnant women (Table 3), the mean serum total calcium level of the postdelivery women (8.78 mg/dL) was below the lower limit of the normal reference range (9 mg/dL). However, despite the relatively low total calcium concentration of the maternal sera, the total calcium concentration of the sera of all of the fetuses was within the normal range.⁷ Similarly, despite the marked hypophosphatemia (3.62 mg/dL) of the mothers at the time of delivery, the phosphorous concentration of fetal blood in each case was within the normal range.⁷

DISCUSSION

This study was undertaken to determine if the pregnancy-associated changes in calcium, vitamin D, and parathyroid hormone in Nigerian pregnant teenagers conform to those that have been documented in older pregnant women living in the same region of West Africa, as well as their counterparts in North America and Europe. Several of the trends in the calcium- and vitamin D-related parameters that were observed in the pregnant teenagers in the present study parallel those reported in other populations of pregnant women. For example, the total serum calcium and albumin concentrations decreased throughout pregnancy such that at the time of delivery, the albumin and the total calcium levels had decreased to 14% and 10%, respectively, of the prepregnancy values.

It is generally recognized^{11,12} that for well-nourished women, the total serum calcium concentration decreases steadily from the first trimester through the late stages of the third trimester (eg, 37 weeks) when values are 5% lower than those of non-pregnant women. This progressive decrease in the total calcium concentration during pregnancy is thought to be caused by a decrease in the serum albumin concentration. It should be noted, however, that the magnitude of the decreases we observed in the serum albumin and total calcium levels in the pregnant Nigerian teenagers were about twice those seen in other studies.^{11,12}

Table 3. Laboratory Data Pertinent to Calcium and Vitamin D in the Controls and Pregnant Teenagers

Parameter	Controls (n=21)	Pregnant Teenagers					
		1st Trimester (n=10)	P Value	2nd Trimester (n=10)	P Value	3rd Trimester (n=10)	P Value
Total calcium (mg/dL)	9.77 (0.32)*	9.30 (0.55)	.02	9.17 (0.32)	.001	8.83 (0.32)	.001
Phosphorous (mg/dL)	4.10 (0.64)	3.86 (0.44)	NS	3.48 (0.57)	.02	3.83 (0.41)	NS
Parathyroid hormone (ng/mL)	0.64 (0.18)	0.60 (0.13)	NS	0.61 (0.17)	NS	0.41 (0.10)	.001
25-hydroxy- vitamin D (ng/mL)	16.1 (3.79)	9.69 (3.23)	.001	17.2 (7.92)	NS	29.8 (10.5)	.001
1,25-dihydroxy- vitamin D (pg/mL)	103 (32.7)	105 (42.5)	NS	141 (36.5)	.01	137 (31.29)	.02

Abbreviations: NS=not significant.

*Numbers in parentheses indicate one standard deviation.

In addition, as reported by others,¹³⁻¹⁵ in the pregnant Nigerian teenagers in this study, the serum concentration of 1,25-dihydroxyvitamin D increased approximately 30% between the first and third trimesters. The serum levels of 25-hydroxyvitamin D increased three-fold in these same pregnant girls over the course of their pregnancies. However, because the dietary intakes of our subjects were not surveyed, we do not know if this rise in serum vitamin D levels during pregnancy was the result of supplementation with vitamin D or increased exposure to sunlight. Previous studies have found that pregnancy per se exerts little influence on serum levels of 25-hydroxyvitamin D.^{16,17}

The trends cited above in our pregnant study groups were to be expected based on the published literature. However, some of our findings were not only unexpected, but also may provide clues regarding the problem of cephalopelvic disproportion often encountered by these young women at delivery. First, although the total calcium levels of the pregnant teenagers were within the normal range of values for North American and European pregnant women, they were nevertheless lower at each stage of pregnancy than the levels reported for populations of non-African women.^{8,12} Second, and more importantly, in the face of a 10% to 15% decline in their total serum calcium levels between the first and third trimesters, the pregnant Nigerian teenagers did not manifest the expected parathyroid hormone response, which is to increase the parathyroid hor-

mone level of the blood.⁸⁻¹⁰ In other words, between the second and third trimesters when the total calcium concentrations had fallen below the lower limit of the normal range to 8.83 mg/dL, the parathyroid hormone level actually decreased by 50% (from 0.61 to 0.41 ng/mL). This observation indicates that a defect in the calcium-parathyroid hormone system may have been present in these pregnant teenagers, one that resulted in hypoparathyroidism in the latter stage of their pregnancies.

The apparent hypoparathyroidism that became evident in our third-trimester study group may have been the result of the moderate degree of malnutrition that the teenage women appeared to have been experiencing. Although the weight gain of the teenage women during gestation was considerable, averaging approximately 17 kg, their serum prealbumin levels were markedly reduced relative to the range of values observed in the privileged, well-nourished control group. It appears from our data, therefore, that the pregnant teenagers studied were not executing the expected maternal adjustments to the demands created during pregnancy by the expanding extracellular fluid volume, and increased calcium loss through urinary excretions and placental transfer to the fetus. While nearly all published reports that address this issue have documented increases in the circulating levels of parathyroid hormone levels during pregnancy, there are a few studies that did not find an increase in parathyroid hormone levels in pregnancy.^{18,19}

1,25-dihydroxyvitamin D is produced by hydroxylation of 25-hydroxyvitamin D in the α -position in a reaction catalyzed by α -hydroxylase, an enzyme whose expression is regulated by parathyroid hormone. Our finding of an increase in the 1,25-dihydroxyvitamin D level during pregnancy in the face of a marked decline in the serum parathyroid hormone level between the second and third trimesters calls into question the hypothesis that "physiologic hyperparathyroidism" is the cause of the increased 1,25-dihydroxyvitamin D one sees during pregnancy.¹⁷

The results of our cord blood analyses are generally in accord with published data. The mean parathyroid hormone level in the blood of the fetuses delivered to the teenage mothers was approximately 30% below those of their mothers. The cord blood levels of 25-hydroxyvitamin D observed in the present study were about 30% lower than the corresponding maternal levels, a finding that has been reported by other investigators.^{9,13,17} In addition, the fetal/maternal ratio for 1,25-dihydroxyvitamin D was 0.51, a value that is in the middle of the range of values observed by others.¹⁷ In light of these findings for the fetal blood specimens we studied, it is not surprising that the fetal/maternal ratio for the total serum calcium values in our study was also in the range of values reported by others. Thus, the problem in the regulation of the parathyroid hormone-vitamin D endocrine system appears to be confined to the teenage mothers as it does not seem to have had adverse effects on the calcium, phosphorous, or 1,25-dihydroxyvitamin D levels of their fetuses.

Comparing the data obtained on pregnant teenagers at the time of delivery in Maiduguri (Table 2) with the corresponding laboratory values acquired in a parallel study performed at approximately the same time in the nearby city of Jos on an older population of women ranging in age from 20 to 29 years (R.H. Glew, October 1997), several differences become readily apparent. First, the total serum calcium levels of the teenage mothers in Maiduguri were lower than those of their older counterparts in Jos (9.2 versus 8.78 mg/dL). Despite this difference in maternal calcium concentrations, the total calcium values of the fetuses born to the two groups of women were indistinguishable (10.5 versus 10.8 mg/dL). Second, although the two groups of pregnant women at the time of delivery had essentially the same 25-hydroxyvitamin D levels (17.8 versus

23.8 ng/mL), the 1,25-dihydroxyvitamin D levels in the teenage group were much higher than those of the older women (130 versus 85.1 ng/mL). The higher levels of the active hormone form of vitamin D in the population of teenage pregnant women at delivery can be explained by the fact that the parathyroid hormone levels in the older group of women (0.30 ng/mL) were significantly lower than those of the teenagers (0.40 ng/mL). The parathyroid hormone levels reported in these two studies were determined in the same laboratory using the same analytical procedure by the same personnel.

SUMMARY

The results of the present study indicate that pregnant teenagers in northern Nigeria become moderately hypocalcemic late in gestation and do not mount the parathyroid hormone response normally seen during pregnancy. These conclusions, taken together with the findings of previous studies of malnourished and rachitic children in Jos, Nigeria, that revealed defects in the parathyroid hormone-vitamin D endocrine system in both groups of children, support the hypothesis that young people in northern Nigeria, from the first few years of life through their teenage years, manifest deficiencies in those mechanisms that regulate blood calcium levels. If this hypothesis is valid, then it follows that normal skeletal development and maturation could be impaired in these children. In the case of young girls who have suffered from a deficiency of calcium and chronic problems affecting the regulation of calcium and vitamin D metabolism, it is conceivable that, ultimately, by the time they begin to bear children, the structure of the female pelvis would be compromised, thereby increasing the risk of cephalopelvic disproportion. Finally, it would be useful and informative to compare the calcium and vitamin D status of pregnant teenagers and adult pregnant women in Maiduguri using a longitudinal paradigm. Such a study is in progress.

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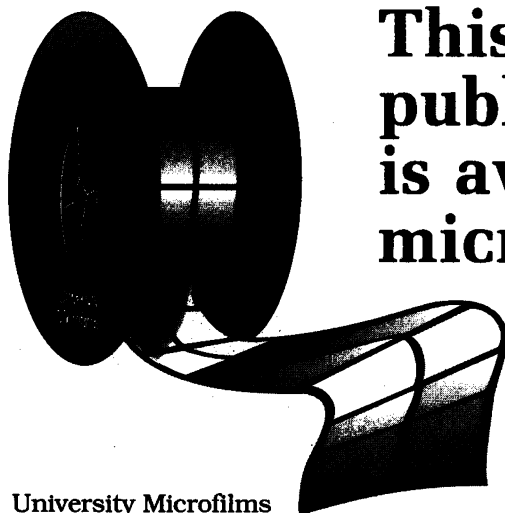
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